II. REMARKS

Formal Matters

Claims 1-7, 9-12, and 25-29 are pending after entry of the amendments set forth herein.

Claims 1-12 and 25-27 were examined and were rejected.

Claim 1 is amended. The amendment to the claim 1 was made solely in the interest of expediting prosecution, and is not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendment to claim 1 is found in the claims as originally filed, and throughout the specification. Accordingly, no new matter is added by this amendment.

Claim 8 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 28 and 29 are added. Support for new claims 28 and 29 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: specification, page 24, lines 10-29. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Objection to the specification

The Office Action stated that the specification is objected to because the specification contains embedded hyperlinks and/or other forms of browser-executable code.

Applicants respectfully request entry of the amendments to the specification noted above, which remove the hyperlinks.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-12 and 25-27 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

The Office Action stated that the specification does not reasonably provide enablement for a) a method of detecting an increased susceptibility to bipolar mood disorder in the general population by detecting any polymorphism between SAVA5 and ga203, wherein any polymorphism associated tih BP indicates in increased susceptibility to develop BP; or b) a method for detecting the presence of any BP

susceptibility DNA polymorphism wherein said method comprises detecting a polymorphism over-represented on disease chromosomes or typing blood relatives to detect the presence of a new polymorphism. The Office Action stated that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims. Applicants respectfully traverse the rejection.

The Office Action stated that the specification is enabling for:

i) methods of detecting an increased susceptibility to bipolar mood disorder (BP) wherein said methods comprise performing a pedigree analysis for the individual's family and analyzing the DNA from family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, D18S1140 and W3422, D18S1140 and ta201, and D18S59 and ta201; and

ii) methods of detecting an increased susceptibility to bipolar mood disorder by assaying for the presence of a 154 bp allele at D18S59 or a 271 bp allele at D18S476, wherein the presence of the alleles is indicative of an increased susceptibility to BP.

As discussed previously, both in responses to Office Actions and in Appellants' Brief, the instant specification provides a description of a number of polymorphisms that were shown, both in a pedigree analysis, and in an analysis of a population of unrelated individuals, to be associated with BP. These polymorphisms are found in a narrow interval on the short arm of chromosome 18, between SAVA5 and ga203. Furthermore, during prosecution, Applicants provided a Declaration of Alison McInnes which showed that several additional polymorphisms were found in this region that also associate with BP. While the specification provides sufficient enablement, and the Declaration of Alison McInnes was further demonstration of this fact, Appellants also provides a publication along with Appellants' Brief which shows that those in the field also found a polymorphism in a gene that is in the same narrow interval (i.e., between SAVA5 and ga203), and that is associated with BP. The evidence presented more than adequately demonstrates that the instant specification is enabling for the full scope of the claims.

Applicants have described in detail how to identify additional polymorphisms associated with BP.

Applicants have described in great detail:

(1) Identification of a narrow interval, between markers SAVA5 and ga203, on the short arm of chromosome 18 which contains polymorphisms associated with BP. This identification was achieved by performing an analysis on a genetically isolated population, as described in detail in the specification. Specification, page 16, line 12 to page 25, line 10.

(2) Identification of polymorphisms, e.g., allele 154 at D18S59, a microsatellite marker polymorphism that associates with BP; and allele 271 at D18S476, another microsatellite marker polymorphism that associates with BP. Specification, page 24, lines 10-29. These polymorphisms associated with BP both in the pedigree and in the population of unrelated individuals. Thus, a number of polymorphisms were identified that are unequivocally associated with BP.

(3) How additional polymorphisms within the defined, narrow region can be identified in other BP patients. Specification, page 27, line 22 to page 29, line 29.

(4) How individuals whose BP status is unknown ("test individuals") can be analyzed for the presence of a polymorphism known to be associated with BP. Specification, page 29, lines 23-29.

The determination of whether a given polymorphism associates with BP was readily performed by those of ordinary skill in the art as of the filing date, given the guidance in the specification and the general knowledge in the art. The methods described in the specification were well known to those skilled in the art as of the filing date. At the time of filing, a number of methods were available to detect polymorphisms, including detection of microsatellilite alleles, and those skilled in the art were well aware of these methods. Linkage disequilibrium analysis to determine whether a given polymorphism is associated with BP is described in ample detail in the instant specification, including working examples. Specification, page 16, line 12 to page 25, line 10.

Applicants provided **working examples** of polymorphisms associated with BP, how such polymorphisms were detected, and how their association with BP was determined. Those skilled in the art could readily find additional polymorphisms in the region on chromosome 18 between SAVA5 and ga203, and determine whether the additional polymorphisms associate with BP, by using the same techniques. As long as the specification discloses at least one method for making and using the claimed

invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C.§112, first paragraph, is satisfied. *In re Fisher*, 166 USPQ 18 (CCPA 1970). Since the application discloses at least one method for detecting polymorphisms in the region of chromosome 18 between SAVA5 and ga203, and teaches how to determine whether any given polymorphism associates with BP, the claims satisfy the enablement requirement of 35 U.S.C.§112, first paragraph.

Those skilled in the art could thus readily identify, using the guidance in the specification, a polymorphism(s) within the identified region that associate with BP. The specification provides both a narrow region that is associated with BP (namely, the region on chromosome 18 between SAVA5 and ga203) as well as polymorphisms within this region that associate with BP. Thus, the specification is indeed enabling for a method of detecting the presence of a BP susceptibility polymorphism in an individual.

The Declaration of Alison McInnes provided further evidence of the fact that those skilled in the art could identify polymorphisms in the SAVA5-ga203 region that are associated with BP without undue experimentation.

The Declaration of Alison McInnes was provided along with the amendment, filed October 10, 2001, responsive to the Final Office Action. The Declaration shows that, using techniques described in the specification, **at least five polymorphisms**, including single nucleotide polymorphisms (SNP), in the narrow interval on chromosome 18p described in the application, are associated with BP. Thus, in addition to the polymorphisms already identified in the patent application, and using the guidance provided in the application, several additional polymorphisms were identified that are associated with BP.

The Office Action asserted that the Declaration of Alison McInnes does not establish that such polymorphisms were identified without undue experimentation. However, the Declaration of Alison McInnes actually provides strong support for the fact that, given the guidance provided in the specification and the knowledge in the art, the claimed methods could indeed be practiced without undue experimentation.

The law is clear that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). See also, Genentech, Inc. v. Novo Nordisk, 42 USPQ 2d 1001 (Fed. Cir. 1997), cert. denied, 522 U.S. 963 (1997); Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991). Furthermore, the courts have taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 227 USPQ 428 (Fed. Cir. 1985). See also, MPEP §2164.01. Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, in Hybritech v. Monoclonal Antibodies, Inc. (231 USPQ 81 (Fed. Cir. 1986)) the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments. Thus, the test of enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine.

The Office Action discussed the Declaration of Alison McInnes, and acknowledged that the Declaration establishes that additional markers were identified that are associated with BP. The Office Action stated that the Declaration "does not establish that such polymorphisms were identified without undue experimentation." Office Action, page 10. To support this assertion, the Office Action stated that "the majority of polymorphisms identified in the stated experiments were not in fact associated with BP," and that even after one has performed the research to identify new polymorphisms in the interval, there is "no predictable means for identifying which of these polymorphisms will be associated with BP." Office Action, page 10. However, the Office Action provided no facts or reasoning to support the assertion that the Declaration does not establish that such polymorphisms were identified without undue experimentation. The experiments described the Declaration of Alison McInnes were performed using guidance in the specification, along with standard laboratory techniques. That the majority of polymorphisms identified are not associated with BP does not lead to a conclusion of lack of enablement. The fact that 5 of the 34 polymorphisms analyzed were found to be associated with BP is

actually a strong indication that the instant specification is enabling, and that the methods can be readily carried out without undue experimentation.

Further evidence that those skilled in the art can identify polymorphisms in the SAVA5-ga203 region that are associated with BP

Given the guidance in the instant specification, those in the field could readily identify polymorphisms associated with BP. Further evidence for the fact that given the guidance in the instant specification, those in the field could readily identify polymorphisms associated with BP was provided in PCT publication WO 99/47535, provided as Exhibit 1 with Appellants' Brief.

WO 99/47535 describes a gene, designated *HKNG1*. This gene is located in the region between SAVA5 and ga203. WO 99/47535 describes mutations in the *HKNG1* gene that are associated with BP. WO 99/47535 provides further evidence for the fact that those skilled in the art could, given the guidance in the instant specification, identify polymorphisms within the SAVA5-ga203 interval that are associated with BP. Thus, WO 99/47535 provides further evidence that the instant specification is enabling.

The Office Action stated that the polymorphism discussed in WO 99/47535 "was identified only because the gene containing this polymorphism was first delineated and characterized." Office Action, page 12. However, the claimed methods do not require characterization of a gene, nor was characterization of a gene a prerequisite for identification of the polymorphism associated with BP discussed in WO 99/47535.

The cited art does not support a conclusion of non-enablement of the instant claims.

The Office Action cited various publications in support of the contention that the teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar (BP) susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field.

The present invention is based on studies that differed from previous studies in several respects. These differences can account for the failure of others, and the success of the present inventors, in finding polymorphisms associated with BP. These differences are can be summarized as follows: (1) others reported **pedigree-based studies**, while the present invention relates to a **population-based study**; (2) others did not use **linkage disequilibrium analysis**; and (3) others **included irrelevant phenotypes**, while the present study **excluded irrelevant phenotypes**. These differences were described in detail in the response to the June 28, 2000 Office Action. *Since the cited studies could not have provided the kind of information that the instant inventors were able to provide, none of the cited art supports a conclusion of non-enablement of the instant claims.*

The Office Action stated that the cited art was cited to show the general unpredictability in the field. However, as discussed previously and above, the cited art cannot properly be used to support a conclusion of lack of enablement of the instant methods, because the cited art ***used different methods*** from those in the instant specification. The Office Action seems to have ignored this fact.

Conclusion

Thus, those skilled in the art, given the guidance in the specification and the general knowledge in the art, would reasonably expect to be able to identify additional polymorphisms within the region between SAVA5 and ga203, and to be able to determine whether such polymorphisms associate with BP. The level of experimentation required would not be undue, because the methods described in the specification were known as of the filing date, and because the specification provides ample guidance.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended to recite a method of detecting an increased susceptibility to bipolar mood disorder comprising performing a pedigree analysis.

Applicants submit that the rejection of claims 1-12 and 25-27 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(a)

Claims 1-12 and 25-27 were rejected under 35 U.S.C.§102(a) as allegedly anticipated by Stine et al. ((1995) *Am. J. Human Genet.* 57:1384-1394; "Stine").

The Office Action stated that Stine teaches methods for detecting microsatellite polymorphisms associated with BP and methods for defining the locus on chromosome 18 that is associated with BP. Applicants respectfully traverse the rejection.

Stine neither discloses nor suggests a method of detecting an increased susceptibility to BP, or a method of detecting the presence of a bipolar mood disorder susceptibility polymorphism in an individual, the method comprising analyzing a sample of DNA from the individual for the presence of a DNA polymorphism on the short arm of chromosome 18 between SAVA5 and ga203. Accordingly, Stine cannot anticipate the instant invention as claimed.

Stine reports a linkage of BP to a pericentromeric region of chromosome 18 (summarized in Stine, Figure 2, page 1391). As discussed in previous responses to Office Actions, Stine did not make any link between D18S59 and BP. Stine reports that the LOD scores for loci on 19p, including D18S59, were "uniformly negative." Stine, page 1388, column 2, first incomplete paragraph. Thus, while the instant invention relates to a narrow, telomeric interval, Stine focused on a pericentromeric region of chromosome 18. Accordingly, Stine cannot anticipate the instant invention as claimed.

Applicants submit that the rejection of claims 1-12 and 25-27 under 35 U.S.C. §102(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

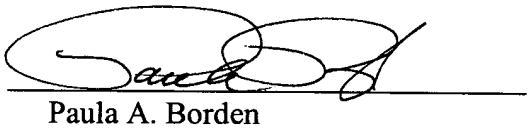
III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL142CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: May 21, 2003

By: 
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